

REMARKS

I. Status of the Claims

Claims 1-8, 32, 41, 50, 60-62, 64, 73-81, 90-93 are pending and stand rejected. Claim 94 has been added.

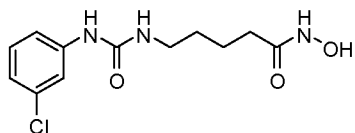
II. Remarks

A. Amendments

New claim 94 recites that R1 may be phenyl or adamantyl. Support for this new claim can be found throughout the specification and in the examples, particularly examples 2, 3, 5, 6, 7 and 8. No new matter has been added.

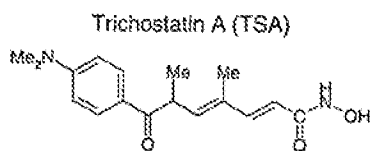
B. Rejections under 35 U.S.C. § 103(a)

The Examiner maintains the rejection of claims 1-8 and 32 as being allegedly unpatentable under 35 U.S.C. 103(a) over Richon et al. Proc. Natl. Acad. Sci. Vol. 95, pp. 3003-7 (1998) (“Richon”) and WO0226696 to Watkins et al. (“Watkins”). The Examiner also refers to Jung et al. 1997, 1999. The Examiner contends that Richon discloses the following compound:

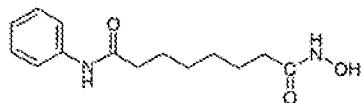


Richon compound 7, 3-Cl-UCHA,

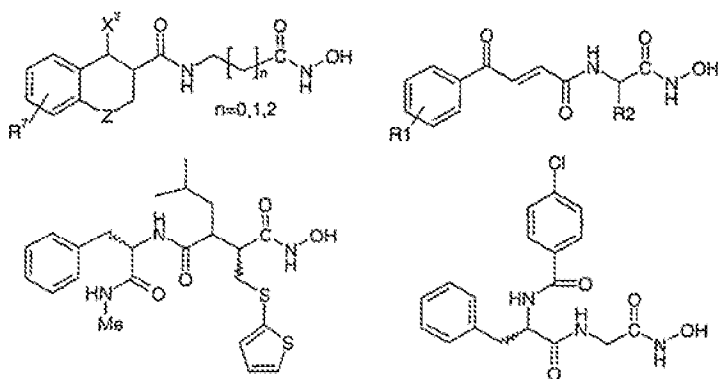
which “differs [from the present claims] in that m is zero,” and further contends that “the use of the compounds is the same.” *Office Action* at p. 4. The Examiner relies on Watkins for describing Trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA):



Suberoylanilide Hydroxamic Acid (SAHA)

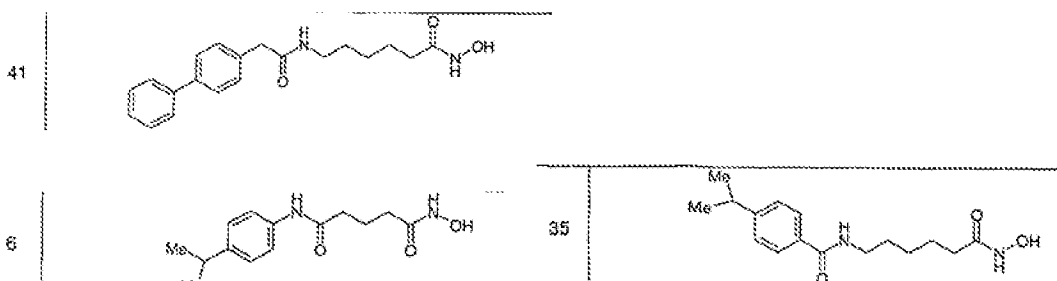


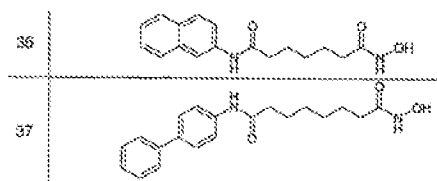
and the following additional compounds:



The Examiner further states that “Watkins refers to the Richon and Jung et al 1997, 1999,” and that Jung et al “teaches that there is a binding region and an enzyme inhibiting group is sep[arated] by a spacer. A variety of spacers are disclosed.” *Id.* at p. 5-6. Based on these teachings, the Examiner concludes that “the link of the phenyl ring can be attached to the N of the urea or to a carbon atom and it would still retain its properties. . . . In other words knowledge of the prior art compounds would have motivated one of skill in the art to modify the chain from m=0 to m=1 to 4, CH₂ linkage to obtain the compound of the instant invention.” *Id.* at p. 6.

The Examiner further states that “similar compounds” are taught by Watkins, and points to 5 has selected, out of all 152 possible variations in structure, the following five compounds:





Applicants traverse.

In order to establish a *prima facie* case of obviousness, the Examiner must determine the scope and content of the prior art, ascertain the differences between the claimed invention and the prior art and resolve the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1 (1966); *see also* Fed. Reg. Vol. 72, No. 195, p. 57529. Once the *Graham* factual inquiries have been resolved, the Examiner must explain why the differences between the cited references and the claims would have been obvious to one of ordinary skill in the art. The Examiner must also show that one of ordinary skill in the art would have a reasonable expectation of success in making the claimed modification. The Supreme Court in *KSR* stressed that “obviousness cannot be sustained by mere conclusory statements; instead there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.” *KSR* 127 S.Ct. 1727, 1740 (2007); *see also* Fed. Reg. Vol. 72, No. 195, p. 57529. Applicants respectfully submit that the Examiner has not met this burden.

The Federal Circuit has recently clarified the application of *KSR* to chemical compound patent claims. In *Eisai Co Ltd v. Dr. Reddy's Laboratories, Ltd.*, Slip op 2007-1397 (Fed. Cir. July 21, 2008), the court pointed out that when analyzing obviousness of a chemical compound, the difference between the claimed compound and the prior art “often turns on the structural similarities and difference between the claimed compound and the prior art.” *Id.* at p. 4. In order to establish that a claimed compound is obvious over a structurally similar compound, there must be: (1) a starting reference point or points in the art, (2) reasons for one skilled in the art to make modifications, and (3) reasons for narrowing the prior art universe to a “finite number of identified, predictable solutions.” *Id.* at p. 8 Thus, there must be “some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e., a lead compound)”. *Id.* (emphasis added).

Additionally, Applicants again direct the Examiner’s attention to *Takeda v. Ranbaxy*, 492 F.3d 1350 (2007). In *Takeda*, applying *KSR*, the Federal Circuit stated “ in cases involving new

chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.” *Id.* at 1361.

Applicants submit that the Examiner has not established any of the aforementioned criteria. First, the Examiner has failed to provide a reasoned identification of a lead compound. Richon describes hybrid polar compounds (“HPC’s”) which inhibit HDAC. *Richon* at abstract. The compounds Richon describes include SAHA, TSA, 3-Cl-UCHA, and several others. *Richon*, Table 1. The HPC’s of Richon have two amides, two esters, two hydroxamic acids, a hydroxamic acid and an amide, an amine and a hydroxamic acid, or a urea and a hydroxamic acid. Out of all of these possible choices, the Examiner chooses 3-Cl-UCHA, which contains a urea and a hydroxamic acid. The Examiner points to no rationale in any cited references for selecting this compound over all of the others, but rather appears to improperly use Applicant’s disclosure as a blueprint for modifying this particular compound of Richon. In fact, according to Richon, TSA is more potent than compound 7. The Examiner has not explained why the skilled artisan would select compound 7 as a lead over TSA, or SAHA or CBHA, for that matter, because Richon provides no such motivation.

The Examiner also states that Watkins “refers to the Richon and Jung et al 1997, 1999,” but fails to explain why Watkins refers to these references. In fact, Watkins cites Richon and Jung along with a laundry list of other references spanning eight pages that describe a myriad of different HDAC inhibitors. *Watkins pp. 5-12*. Watkins does not in any way single out Richon or Jung as describing potential lead compounds. Watkins describes 152 different compounds, yet the Examiner has selected, out of all of these possible variations in structure, compounds 41, 6, 35, 36 and 37. As with Richon, the Examiner provides no basis in the art for singling out these particular compounds. Indeed, several compounds of Watkins show even greater activity than the Examiner’s selected compounds, e.g., 105, 110, and 129, to name only a few. The only basis for selecting these compounds could be Applicant’s present disclosure, which of course, is impressive hindsight reasoning.

The Examiner also has not provided reasons to modify either compound 7 of Richon by carbon homologation, or any of the Watkins compounds by changing an amide group to a urea. Nor has the Examiner provided any evidence that these changes represent a “finite number of identified, predictable solutions.” The Examiner contends that “the prior art teaches that the phenyl ring can be

attached to the N of the urea or to a carbon atom [of an amide] and it would still retain its properties.” *Office Action* at p. 6. Applicants submit that even if this statement were true, it still does not provide the requisite motivation to make this change, particularly in view of the numerous different possible ways of modifying these compounds presented in the cited references.

For at least these reasons, Applicants submit that the present claims are not obvious over either Watkins or Richon, or the combination of these references.

C. Rejections under 35 U.S.C. § 112, first paragraph

The Examiner maintains the rejection of claims 1-8 and 32 as being allegedly unpatentable under 35 U.S.C. § 112, first paragraph, for a lack of an enabling disclosure. *Office Action* at p. 12. The Examiner contends that the present rejection under § 112, first paragraph, is based on “make and use,” and that Applicants have not enabled the use of these compounds because pharmaceutically uses are allegedly “unpredictable.” *Office Action* at p. 13. Specifically, the Examiner contends that the specification “while being enabling for R1 to be a phenyl and adamantyl, does not reasonably provide enablement for any other cycloalkyl or any 3-10 membered heterocyclic group.” *Id.* at p. 10. The Examiner alleges, without any support, that “[a] heterocyclic group or a cycloalkyl group would definitely be different than an phenyl or adamantyl and as such should have more showing that it is a ‘pharmaceutical’” *Office Action* at p. 9. Applicants respectfully traverse this rejection.

As an initial matter, Applicants submit that at least new claim 94, in which R¹ is phenyl or adamantyl, obviates the Examiner’s enablement rejection.

35 U.S.C. §112, first paragraph, requires that a patent must enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); M.P.E.P. § 2164.01. Nevertheless, “the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.” M.P.E.P. § 2164.01. In order to make a rejection for lack of enablement, the Examiner first bears the burden of establishing “a reasonable basis to question the enablement provided for the claimed invention. M.P.E.P. § 2164.04 (citing *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993)). Furthermore, a specification “which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in

describing and defining the subject matter sought must be taken as being in compliance with the enablement requirement . . . , unless there is a reason to doubt the objective truth of the statements contained therein” M.P.E.P. § 2164.04. It is also well-established that Applicants need not “necessarily describe how to make and use every possible variant of the claimed invention, for the artisan’s knowledge of the prior art and routine experimentation can often fill in gaps.” *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003).

Applicants submit that the Examiner has applied an erroneous legal standard in rejecting the present claims for lack of enablement, and has furthermore ignored Applicant’s factual-based evidence of enablement. Under the Wands analysis, the present claims are more than sufficiently enabled, as explained below.

Several factors are considered in determining whether any experimentation is undue, including: 1) the breadth of the claims; 2) the nature of the invention; 3) the state of the prior art; 4) the level of one of ordinary skill; 5) the level of predictability in the art; 6) the amount of direction provided by the inventor; 7) the existence of working examples; and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d at 737; M.P.E.P. 2164.01(a).

1. The breadth of the claims

Regarding the first Wands factor, the Examiner contends that the claims encompass “very wide range of compounds.” Applicants respectfully disagree that the present claims are unduly broad. Furthermore, as explained in more detail below, the breadth of the instant claims are fully enabled by the specification.

2. The nature of the invention

Regarding the second *Wands* factor, the nature of the invention, the Examiner merely states “the invention is a substituted compound that is useful to treat cancer.” *Office Action mailed May 8, 2006*, at p. 3. The Examiner does not explain how this factor supports an enablement rejection.

3. The state of the prior art and the level of predictability in the art

Regarding the third *Wands* factor, the Examiner contends that the state of the prior art involves screening *in vitro* and *in vivo*, and that there is “no absolute predictability and no

established correlation between the different substitutions on a core that they would all behave in the exact same way.” *Office Action*, at p. 13(emphasis added). Regarding the fifth *Wands* factor, the Examiner alleges that the pharmaceutical art is unpredictable, “requiring each embodiment to be individually assessed for physiological activity.” *Id.* The Examiner further alleges that “there is no absolute predictability and no established correlation between in vitro activity and the treatment of any and all cancers.” *Id.*

The Examiner’s analysis of the third and fifth wands factors contains several erroneous legal standards. Applicants have repeatedly pointed out errors in the Examiner’s enablement analysis, and the Examiner has repeatedly ignored these arguments and refuse to apply an appropriate standard of analysis. *See Responses* filed on October 31, 2007, March 26, 2007, and September 11, 2006.

In fact, the Examiner now relies on two references, Methot and Siliphaivanh, to establish that “all structures do not have the same activity.” *Office Action* at p. 7-8. The Examiner contends that Methot demonstrates that the HDAC activity changes when a heterocyclyl group is substituted for an aryl group. Applicants are not required to demonstrate that all structures have the same activity. If anything, Methot and Siliphaivahn support a finding of enablement because even though there were some differences in levels of activity, the Methot and Siliphaivahn compounds all still, nevertheless, did demonstrate at least some HDAC activity.

Furthermore, the Examiner’s apparent requirement that Applicants individually assess each embodiment of the present claims has no basis in the M.P.E.P. nor in the case law. The C.C.P.A. has explicitly stated that patent applicants are “**not required to disclose every species encompassed by their claims even in an unpredictable art**” in order to satisfy the enablement requirement. *In re Angstadt*, 537 F.2d 489, 502 (C.C.P.A. 1976) (emphasis added). Working examples are not even necessarily required to enable an invention. *In re Long*, 368 F.2d 892, 895 (C.C.P.A. 1966)(holding that the absence of a working example does not in and of itself compel a finding of non-enablement). The Examiner misinterprets *In re Fisher*, 427 F.2d 833 (CCPA 1970). *Fisher* merely found that an applicant had not enabled the full claimed potency range of a particular compound. In particular, the applicant had disclosed a potency range of 1.11 to 2.30 international units, but tried to claim a range of greater than 1. The court found that the applicant in that case was

not entitled to the open-ended range of greater than 1. Thus, the Examiner's reliance on *Fisher* for the proposition that each compound must be assessed for activity is in error.

Additionally, "absolute predictability" is not required, nor must Applicants demonstrate that each compound "behave[s] in the exact same way." See *Office Action* at p. 13. Applicants respectfully request that the Examiner apply the correct legal standard in assessing enablement.

The Examiner contends that Applicants numerous *in vitro* examples in the specification do not sufficiently enable the skilled artisan to "use" the claimed invention. *Id.* To the contrary, *in vitro* models are more than adequate to establish enablement of compounds, and often are sufficient to establish *in vivo* activity, even for method of treatment claims. *In re Brana*, 51 F.3d 1560, 1565 (Fed. Cir. 1995); see also M.P.E.P. 2164.02. The Federal Circuit in *Brana* held that *in vitro* tumor models were sufficiently enabling for the treatment of cancer. Similarly, the *in vitro* data of HDAC inhibition, cytotoxicity in SQ-20B cells, and radiation clonogenic survival rates assays described in the instant specification sufficiently enable the use of the presently claimed compounds. *Specification* at Tables 3 and 4. As explained in the specification, HDAC inhibitors are known in the art as sensitizing agents in radiation therapy, *Specification* at p. 3. The data presented in Tables 3 and 4 confirm this fact. Accordingly, the presently claimed compounds would be expected to be useful in inhibition of HDAC activity, increasing sensitivity of cancer cells to the cytotoxic effects of radiation and the treatment of cancer. Thus, at least compound claims 1-8 and 32 are enabled by the instant specification.

Indeed, Applicants direct the Examiner's attention to the case law which has recognized the advances in the art with respect to cancer treatment. The C.C.P.A. noted in its decision in *In re Jolles* that "medical treatment of a specific cancer is not such an inherently unbelievable undertaking or involves such implausible scientific principles as to be incredible." *In re Jolles*, 628 F.2d 1322, 1327 (C.C.P.A.). The Board also has recognized that "[t]he state of the art of cancer treatment has advanced markedly since the time of the decision in *In re Citron* . . . as reflected in the decision *In re Jolles*." *Ex parte Krepelka* U.S.P.Q. 746, 747 (Bd. Pat. App. & Int. 1986). Finally, the Federal Circuit in *In re Brana* noted that "[m]odern science has previously identified numerous successful chemotherapeutic agents. *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1995). This line of cases demonstrates that the Board and the courts recognize the significant advances in cancer treatment in recent years.

For the reasons set forth above, Applicants submit that factors 3 and 5 also support enablement of the instant claims.

4. The level of ordinary skill

With respect to the fourth *Wands* factor, the ordinary artisan is highly skilled, as the Examiner previously noted. *Office Action mailed May 8, 2006*, at p. 3. Therefore, the fourth factor also supports a finding of enablement.

5. The amount of direction provided by the inventor

Regarding the sixth *Wands* factor, the Examiner states that the inventors provide “little direction in the instant specification,” and further contends that that all of the compounds shown in Tables 3 and 4 of the instant application have either a phenyl or adamantyl, and do not cover the scope of the claimed genus of aryl, cycloalkyl and heterocyclyl. *Office Action* at p. 3. To the contrary, examples 1-8, depicted in Tables 3 and 4, in fact include examples of both aryl and substituted aryl (e.g., dimethylaminophenyl), as well as cycloalkyl (e.g., adamantyl). In Applicants’ previous response, Applicants pointed to synthetic scheme I (Specification p. 31), demonstrating that the preparation of such compounds has indeed been enabled. *Response mailed September 8, 2006*. This evidence establishes that those skilled in the art would readily know make the claimed compounds based on the guidance provided in the instant application. The Examiner has not denied that Scheme I, in addition to examples 1-8, sufficiently enable the skilled artisan to make the presently claimed compounds.

Nevertheless, the Examiner contends that the present rejection under § 112, first paragraph, is based on “make and use,” and that Applicants allegedly have not enabled the use of these compounds because pharmaceutically uses are allegedly “unpredictable.” *Office Action* at p.10. As discussed above, Applicants data establishes HDAC inhibition, cytotoxicity and increased radiation sensitivity in compounds having aryl, substituted aryl and cycloalkyl groups, as well as compounds having varied values for m and n. *Specification* at Tables 3 and 4.

6. The existence of working examples and the quantity of experimentation needed to make and use the invention

Regarding the seventh and eighth Wands factors, the Examiner states that “there are no working examples nor any in[]vitro nor in vivo data.” *Office action* at p. 13. This statement is plainly erroneous. As explained in detail above, the specification provides many working examples, including *in vitro* data demonstrating HDAC inhibition, cytotoxicity in SQ-20B cells, and radiation clonogenic survival data for compounds encompassed by the instant claims. *Specification* at Tables 3 and 4.

Applicants again stress that the Examiner’s analogy to caffeine and theophylline is inaccurate. *Office Action* at p. 9. The Examiner continues to rely on this irrelevant and factually incorrect analogy, despite the references submitted by applicants in the response filed on March 26, 2007. In the previous response, Applicants demonstrated that theophylline and caffeine have both similar structure and activity. (See Snyder et al.; Chapman et al; and Wikipedia Attached to response filed March 26, 2007). These references demonstrate that the xanthine class of compounds, as a whole, possess similar biological activity. For example, Snyder et al. demonstrates that caffeine and theophylline have several biological activities in common, such as the reversal of L-PIA evoked depression and stimulation of locomotor activity (see Abstract and Fig. 1), and hypothesizes that the entire class of xanthines exhibits behavioral stimulant effects due to the blockade of central adenosine receptors (Abstract). Chapman et al. notes that caffeine “shares a variety of its pharmacological properties with the other naturally occurring methylxanthines, theophylline and theobromine. (Chapman at 616, ll. 2-17.) According to Wikipedia, theophylline “bears structural and pharmacological similarity to caffeine.” (Wikipedia, Theophylline, at p. 1).

Nevertheless, the Examiner states that “[c]affeine even though structurally so similar . . . is not marketed as a bronc[h]odilator.” *Office Action* at p. 9. The fact that caffeine is not *marketed* as a bronchodilator does not negate the scientifically established fact that it has similar activity to theophylline. Thus, the theophylline/caffeine comparison demonstrates that, contrary to the Examiner’s contention, those skilled in the art would expect the presently claimed genus of compounds to possess similar activity.

For at least the reasons set forth above, Applicants submit that the instant claims are fully enabled in accordance with 35 U.S.C. § 112, first paragraph.

III. Conclusion

In light of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. Reconsideration and timely allowance of the pending claims is respectfully solicited. If a telephone interview would be helpful, the Examiner is invited to call the undersigned at 617-832-1223. Applicants hereby request that any additional fees required for timely consideration of this application be charged to **Deposit Account No. 06-1448, GUX-012.01.**

Dated: November 25, 2009

Respectfully submitted,

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